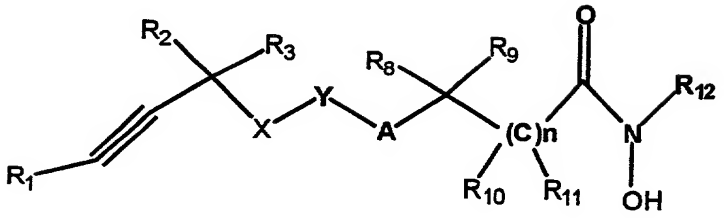
CLAIMS

What is claimed:

1. A compound of formula



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wherein:

R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-8 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or -C4-C8-cycloheteroalkyl;

R_2 and R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH;

R_7 is hydrogen, aryl, aralkyl, heteroaryl, heteroaralkyl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, $-C(O)-R_1$, $-SO_2-R_1$, $-C(O)-NHR_1$, $-C(O)NR_5R_6$, $-C(O)R_1NR_5R_6$, $-C(O)-OR_1$, $-C(NH)-NH._2$.

R_8, R_9, R_{10}, and R_{11} are each, independently, hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C4-C8-cycloheteroalkyl, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms; with the proviso that one of the pairs R8 and R9, R9 and R10 or R10 and R11, together with the carbon atom or atoms to which they are attached, form a cycloalkyl ring of 3-6 carbon atoms, or a -C4-C8-cycloheteroalkyl ring;

R_{12} is hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C_4-C_8-cycloheteroalkyl, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO_2, NR_7, or CH_2;

X is O, S, SO, SO_2, NR_7, or CH_2;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein Y is phenyl, pyridyl, thienyl, furanyl, imidazolyl or triazolyl or thiadiazolyl.

3. A compound of Claim 1 selected from the group consisting of:
1-(4-Bromo-benzyl)-4-(4-but-2-ynyxoy-benzenesulfonyl)-piperdine-4-carboxylic acid hydroxyamide;
4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(4-methoxy-benzyl)-piperdine-4-carboxylic acid hydroxyamide;
4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(4-chloro-benzyl)-piperdine-4-carboxylic acid hydroxyamide;
1-Benzyl-4-(4-but-2-ynyloxy-benzenesulfonyl)-piperdine-4-carboxylic acid hydroxamide;
1-(4-Bromo-benzyl)-4-(4-pent-2-ynyloxy-benzenesulfonyl)-piperdine-4-carboxylic acid hydroxyamide;
1-(4-Bromo-benzyl)-4-(4-oct-2-ynyloxy-benzenesulfonyl)-piperdine-4-carboxylic acid hydroxyamide;
4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(4-fluoro-benzyl)-piperdine-4-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(4-cyano-benzyl)-piperidine-4-carboxylic acid hydroxamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(4-methyl-benzyl)-piperidine-4-carboxylic acid hydroxamide;

4-(4-But-2-ynyloxy-benzenesulfonyl)-1-(3,4- dichloro-benzyl)-piperidine-4-carboxylic acid hydroxamide;

1-(4-Bromo-benzyl)-4-(4-prop-2-ynyloxy-benzenesulfonyl)-piperdine-4-carboxylic acid hydroxyamide;

1-(4-Bromo-benzyl)-4-[4-(4-piperdin-4-yl-but-2-ynyloxy)-benzenesulfonyl]-piperdine-4-carboxylic acid hydroxyamide;

1-(4-Bromo-benzyl)-4-[4-(4-morpholin-4-yl-but-2-ynyloxy)-benzene-sulfonyl]-piperdine-4-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-phenylsulfanyl)-4-hydroxycarbamoyl-piperidine-1-carboxylic acid tert-butyl ester;

4-(4-But-2-ynyloxy-phenylsulfanyl)-piperidine-4-carboxylic acid hydroxyamide

1-(4-Bromo-benzyl)-4-(4-but-2-ynyloxy-phenylsulfanyl)-piperidine-4-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-phenylsulfanylmethyl)-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-benzenesulfonylmethyl)-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

4-(4-But-2-ynyloxy-benzenesulfinylmethyl)-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxytetrahydro-2H-pyran-4-carboxamide;

1-benzyl-4-{[3-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-4-piperdine carboxamide;

4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-1-isopropyl-4-piperidine carboxamide;

4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-1-(3-pyridinylmethyl)-4-piperidine carboxamide;

3-{[4-(2-Butynyloxy)phenyl]sulfonyl}-1-ethyl-N-hydroxy-3-piperidine-carboxamide;

3-{[4-(2-butynyloxy)phenyl]sulfonyl}-1-(4-chlorobenzyl)-N-hydroxy-3-piperidinecarboxamide;

4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-piperidine-4-carboxylic acid hydroxyamide;

4-{[4-(2-Butynyloxy)phenyl]sulfonyl}-1-(3-pentanyl)-piperidine-4-carboxylic acid hydroxyamide;

1-(4-Methoxy-benzyl)-4-(4-prop-2-ynyloxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide;

1-(4-Chloro-benzyl)-4-(4-prop-2-ynyloxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide;

tert-butyl-4-({[4-(2-butynyloxy)phenyl]sulfanyl}methyl)-4-[(hydroxyamino)-carbonyl]-1-piperidinecarboxylate;

4-({[4-(But-2-ynyloxy)phenyl]thio}methyl)-N-hydroxypiperidine-4-carboxamide;

tert-Butyl-4-({[4-(2-butynyloxy)phenyl]sulfinyl}methyl)-4-[(hydroxyamino)-carbonyl]-1-piperidinecarboxylate;

4-[[[4-(2-Butynyloxy)phenyl]sulfinyl]methyl]-N-hydroxy-4-piperidine-carboxamide;

tert-Butyl-4-({[4-(but-2-ynyloxy)phenyl]sulfonyl}methyl)-4-[(hydroxyamino)-carbonyl]piperidine-1-carboxylate;

tert-butyl-4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-4-[(hydroxyamino)-carbonyl]-1-piperidinecarboxyla;

1-Acetyl-4-[[[4-(2-butynyloxy)phenyl]sulfonyl]methyl]-N-hydroxy-4-piperidinecarboxamide;

1-(2-Butynyl)-4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-4-piperidinecarboxamide hydrochloride;

N-1-(tert-Butyl)-4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-N-4-hydroxy-1,4-[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-N-4-hydroxy-1,4-l]sulfonyl}-methyl)-N~4~-hydroxy-1,4-piperidinedicarboxamide;

Methyl 4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-4-[(hydroxyamino)-carbonyl]- 1-piperidinecarboxylate;

Benzyl 4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-4-[(hydroxyamino)-carbonyl]- 1-piperidinecarboxylate;

1-Benzyl-4-({[4-(2-butynyloxy)phenyl] sulfonyl} methyl)-N-hydroxy-4-butynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-4-piperidinecarboxamide;

4-({[4-(2-Butynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-[(2,2,5-trimethyl-1,3-dioxan-5-yl)carbonyl]-4-piperidinecarboxamide;

4-({[4-(2-Butynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoyl]-4-piperidinecarboxamide;

1-[Amino(imino)methyl]-4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-4-l]-4-({[4-(2-butynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-4-oxy)phenyl]sulfonyl}methyl)-N-hydroxy-4-piperidinecarboxamide;

4-({[4-(2-Butynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-(4-hydroxy-2-butynyl)- henyl]sulfonyl}methyl)-N-hydroxy-1-(4-hydroxy-2-butynyl)-4-piperidinecarboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-1-ethyl-N-hydroxypiperidine-4- carboxamide triflouroacetic acid salt;

2-chloro-5-(chloromethyl) thiophene4-({[4-(But-2-ynyloxy)phenyl]-sulfonyl}-methyl)-1-[(5-chlorothien-2-yl)methyl]-N- hydroxypiperidine-4-carboxamide triflouroacetic acid salt;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-(pyridin-4-ylmethyl)piperidine-4-carboxamide triflouroacetic acid salt;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-(pyridin-3 ylcarbonyl)piperidine-4-carboxamide triflouroacetic acid salt;

1-Benzoyl-4-({[4-(but-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-piperidine-4- carboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-(thien-2-ylcarbonyl) piperidine-4-carboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-1-ethyl-N-4-hydroxy-piperidine-1,4-dicarboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-4-hydroxy-N-1- phenyl-piperidine-1,4-dicarboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-1-,N-1-diethyl-N-4-hydroxypiperidine-1,4-dicarboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-(morpholin-4-ylcarbonyl)piperidine-4-carboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-4-hydroxy-N-1-methyl-N-1-phenylpiperidine-1,4-dicarboxamide;

Octyl-4-({[4-(but-2-ynyloxy)phenyl]sulfonyl}methyl)-4-[(hydroxyamino)-carbonyl] piperidine-1-carboxylate;

4-Methoxyphenyl4-({[4-(but-2-ynyloxy)phenyl]sulfonyl}methyl)-4-[(hydroxy-amino) carbonyl]piperidine-1-carboxylate;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-(phenylsulfonyl) piperidine-4-carboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-[(1-methyl-1H-imidazol-4-yl)sulfonyl]piperidine-4-carboxamide;

1-[2-(Benzylamino)acetyl]-4-({[4-(but-2-ynyloxy)phenyl]-sulfonyl}methyl)-N-hydroxypiperidine-4-carboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-(2-morpholin-4-ylacetyl)piperidine-4-carboxamide;

4-({[4-(But-2-ynyloxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-[2-(4-methyl-piperazin-1-yl)acetyl]piperidine-4-carboxamide;

1-Acetyl-4-(4-but-2-ynyloxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxamide;

1-Benzoyl-4-(4-but-2-ynyloxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxamide;

1-(4-Methoxybenzoyl)-4-(4-but-2-ynyloxy benzenesulfonyl)piperidine-4-carboxylic acid hydroxamide;

4-(4-But-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-(pyrrolidine-1-carbonyl)-4-piperidinecarboxamide;

Ethyl 4-(4-but-2-ynyloxybenzenesulfonyl)-4-[(hydroxyamino)carbonyl]-1-piperidinecarboxylate;

4-(4-But-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-[(trifluoromethyl)sulfonyl]-4- piperidinecarboxamide;

4-(4-But-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-(3-pyridinylcarbonyl)- 4-piperidinecarboxamide;

4-(4-but-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-(2-thienylcarbonyl)- 4-piperidinecarboxamide;

4-(4-but-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-[(4-methoxyphenyl)-sulfonyl]-4-piperidinecarboxamide;

4-(4-but-2-ynyloxybenzenesulfonyl)-N-hydroxy-1-[(2,2,5-trimethyl-1,3-dioxan-5-yl)carbonyl]-4-piperidinecarboxamide;

Tert-butyl-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-4-[(hydroxyamino)carbonyl]-1-piperidinecarboxalate;

4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-4-piperidinecarboxamide hydrochloride;

Methyl ({4-{[4-(2-butynyloxy)phenyl]sulfonyl}-4-[(hydroxyamino)carbonyl]-1-piperidinyl}methyl)benzoate hydrochloride;

4-({4-{[4-(2-butynyloxy)phenyl]sulfonyl}-4-[(hydroxyamino)carbonyl]-1-piperidinyl}methyl)benzoic acid hydrochloride;

1-[4-(Aminocarbonyl)benzyl]-4-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-4-piperidinecarboxamide hydrochloride;

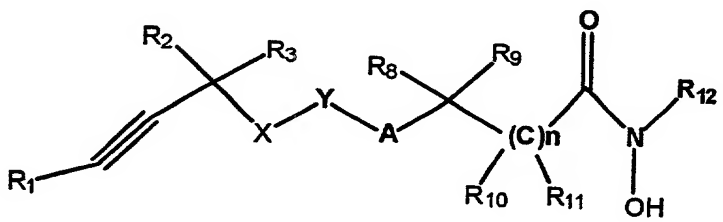
Tert-butyl 4-{[4-(but-2-ynyloxy)phenyl]sulfinyl}-4-[(hydroxyamino)-carbonyl]piperidine-1-carboxalate;

4-(4-(But-2-ynyloxy-benzenesulfinyl)-piperidine-4-carboxylic acid hydroxamide hydrochloride; and

1-(4-Bromo-benzyl)-4-(4-But-2-ynyloxy-benzenesulfinyl)-piperidine-4-carboxylic acid hydroxamide hydrochloride;

and pharmaceutical salts thereof.

4. A method of inhibiting pathological changes mediated by TNF-α converting enzyme (TACE) in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a compound having the formula



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wherein:

R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-8 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or -C4-C8-cycloheteroalkyl;

R_2 and R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH;

R_7 is hydrogen, aryl, aralkyl, heteroaryl, heteroaralkyl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, $-C(O)-R_1$, $-SO_2-R_1$, $-C(O)-NHR_1$, $-C(O)NR_5R_6$, $-C(O)R_1NR_5R_6$, $-C(O)-OR_1$, $-C(NH)-NH_2$.

R_8, R_9, R_{10}, and R_{11} are each, independently, hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C4-C8-cycloheteroalkyl, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms; with the proviso that one of the pairs R8 and R9, R9 and R10 or R10 and R11, together with the carbon atom or atoms to which they are attached, form a cycloalkyl ring of 3-6 carbon atoms, or a -C4-C8-cycloheteroalkyl ring;

R_{12} is hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C4-C8-cycloheteroalkyl, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO_2, NR_7, or CH_2;

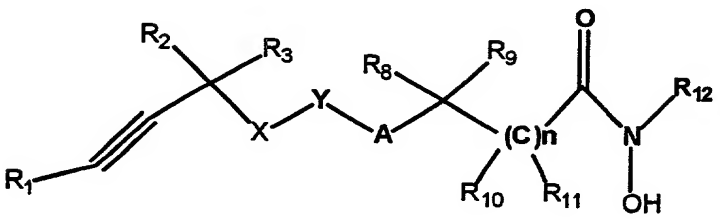
X is O, S, SO, SO_2, NR_7, or CH_2;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

5. The method of Claim 4 wherein the condition treated is rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV infection.

6. A pharmaceutical composition comprising a compound having the formula



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wherein:

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R_2 and R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH;

R_7 is hydrogen, aryl, aralkyl, heteroaryl, heteroaralkyl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, $-C(O)-R_1$, $-SO_2-R_1$, $-C(O)-NHR_1$, $-C(O)NR_5R_6$, $-C(O)R_1NR_5R_6$, $-C(O)-OR_1$, $-C(NH)-NH_2$.

R_8, R_9, R_{10}, and R_{11} are each, independently, hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C4-C8-cycloheteroalkyl, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms; with the proviso that one of the pairs R8 and R9, R9 and R10 or R10 and R11, together with the carbon atom or atoms to which they are attached, form a cycloalkyl ring of 3-6 carbon atoms, or a -C4-C8-cyclohèteroalkyl ring;

R_{12} is hydrogen, aryl or heteroaryl, cycloalkyl of 3-6 carbon atoms, -C_4-C_8-cycloheteroalkyl, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO_2, NR_7, or CH_2;

X is O, S, SO, SO_2, NR_7, or CH_2;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and

n is 0-2; or a pharmaceutically acceptable salt thereof.